Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. The pending claims have been amended for clarity to remove references to Figures and to the extracellular domain; they now refer to the SEQ ID NOs alone. Entry of these amendments is respectfully requested. Claims 39-41 and 47 have been canceled without prejudice or disclaimer. Claims 42-46 and 49-51 are pending and remain rejected in this application. The rejections to the claims are respectfully traversed.

Request for consideration of change of address

A revocation of Power of Attorney and change of address was mailed to the USPTO in this case on February 20, 2003. A stamped, return postcard was received from the USPTO dated February 27, 2003. Applicants respectfully request that the Examiner note the address change and kindly direct all correspondence pertaining to this case to Heller Ehrman White and McAuliffe LLP, 275, Middlefield Road, Menlo Park, CA 94025.

Claim Rejections – 35 USC § 101 and 112, First Paragraph

Claims 39-47 and 49-51 are rejected under 35 U.S.C. §101 allegedly because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility.

Claims 39-47 and 49-51 are rejected under 35 U.S.C. §112, first paragraph, allegedly since the claimed invention is not supported by either a clear asserted utility or a well established utility, one in the art clearly would not know how to use the claimed invention.

Initially, Applicants submit that any references made to polypeptides other than PRO266 in previous responses was done in error.

The Examiner maintains that "the assay fails to provide any explanation regarding a correlation of this assay and any real life diseases". The Examiner further asserts that "one skilled in the art readily understands that the assay described in Examples 74 and 77 is what is called in pharmacology, a toxicity test". For the reasons described below, Applicants respectfully traverse.

Without acquiescing to the propriety of this rejection, but merely to expedite prosecution in this case, Applicants hereby file an executed Declaration by Sherman Fong, Ph.D., an expert in the field of immunology, that discusses, in detail, the skin vascular permeability assay, and shows that this assay and its modifications have been used, widely, in the art. Dr. Fong explains the mechanism by which such inflammation occurs in his declaration:

> "Proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. These proinflammatory molecules recruit cells like leukocytes which includes monocytes, macrophages, basophils, and eosinophils. These cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. How leukocytes exit the vasculature and move to their appropriate destination of injury or infection is critical and is tightly regulated. Leukocytes move from the blood vessel to injured or inflamed tissues by rolling along the endothelial cells of the blood vessel wall and then extravasate through the vessel wall and into the tissues (see Exhibit B). This diapedesis and extravasation step involves cell activation and a stable leukocyte-endothelial cell interaction."

Thus, proinflammatory molecules display blemishes of a previously injected marker dye in this assay, and an example of a positive reaction with a test proinflammatory molecule like PRO266 is shown in Exhibit I. Therefore, contrary to the Examiner's assertion, this assay is not a toxicity test but has routinely been used to identify several well-known proinflammatory molecules like blood coagulation factor XIII, VEGF, etc. In this assay, the results were further analyzed by histopathological examination to rule out inflammation due to endothelial cell damage or mast cell degranulation (see declaration). Hence, the vascular permeability observed was not due to histamine release or endothelial cell damage.

Utilities for PRO266 are also discussed by Dr. Fong in his declaration, based on a positive score in the skin vascular permeability assay; for example, to treat inflammatory diseases like autoimmune diseases. Such utilities would readily be understood, and accepted as substantial, credible and specific utilities by those skilled in the art at the effective filing date, based on the instant disclosure and the advanced knowledge in the art regarding this assay.

Further, since Applicants have asserted that PRO266 is an inflammatory molecule useful for treating inflammatory conditions like autoimmune diseases, one skilled in the art would know how to make and use the invention without undue experimentation, since the act of performing experiments in clinical situations is considered routine and is well-established in the art. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 39-47 and 49-51 are rejected under 35 U.S.C. §112, first paragraph, allegedly as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention.

Claims 39-41 have been canceled and hence this rejection is moot with respect to these claims. Applicants respectfully traverse the rejection with respect to the remaining claims.

Whether a specification shows that Appellants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including level of knowledge and skill in the art, and teaching provided by the specification. The inventor is not required to describe every single detail of his invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention is from the field of recombinant DNA technology. In particular, the invention defined by the claims rejected concerns isolated polypeptides having 95%, or 99% sequence identity with a particular disclosed polypeptide sequence. In addition, the claims have now been amended to recite that the polypeptides claimed induces an inflammatory response. It is well established that the level of skill in this field is relatively high, and is represented by a Ph.D. scientist having several years of experience in the pertinent field. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The written description requirements are well-explained in Example 14 of the Written Description guidelines issued by the U.S. Patent Office. The instant specification evidences actual reduction to practice of full-length native human PRO266 polypeptide (SEQ ID NO: 91),

with or without its signal sequence. In addition, the specification provides detailed description about the cloning and expression of variants of the polypeptide PRO266 (see, e.g. pages 154-155 and 196-201), and describes an assay for testing the ability of a PRO266 polypeptide, including variants of the native sequence, to induce a proinflammatory response. Thus, Applicants indicate that the genus of proteins that are variants of PRO266 must also possess the an ability to induce a proinflammatory response and must have at least 95% identity to the sequence of SEQ ID NO: 91. In view of this disclosure of the proinflammatory assay which is useful for identifying the variants with at least 95% identity SEQ ID NO: 91, a person skilled in the art would recognize that Applicants were in possession of the members of the genus which have the necessary common attributes as described at the effective filing date of the present application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 39-47 and 48-51 were rejected under 35 U.S.C. §112, second paragraph, allegedly, as being indefinite for reciting "the polypeptide...lacking its associated signal peptide" and "the extracellular domain...lacking its associated signal sequence, parts (b) and (d)." Claims 45 and 49-52 were indefinite for being dependent from indefinite claims.

Without acquiescing to the propriety of this rejection, Applicants have deleted references to the extracellular domain in the pending claims. Further, Applicants submit that the PRO266 protein sequence shown in Figure 34 of the instant application, discloses a signal sequence from amino acid 1-15. Accordingly, the amended claims, are believed to be definite and Claims 45 and 49-51 are definite as well. Hence, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C29). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 27, 2004

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